Studies on Cardiotonic Agents. III.[1] Synthesis of 1-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]-3-substituted 2-Imidazolidinone and 2-Imidazolidinethione Derivatives

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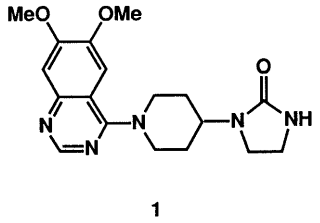
A series of 1-[1-(6,7-dimethoxy-4-quinazolinyl)-4-piperidinyl]-3-substituted 2-imidazolidinone and 2-imidazolidinethione derivatives was synthesized and examined for cardiotonic activity in anesthetized dogs. Alkylation of the 2-imidazolidinone (1) afforded the *N*-alkylated products, while alkylation of the 2-imidazolidinethione (12) afforded the *S*-alkylated derivatives accompanied with a small quantity of the *N*-alkylated products. The *N*-alkylated derivatives showed generally potent activity, and the *S*-alkylated ones exhibited weak activity. Insertion of an alkyl group between the piperidine and the imidazolidinone moiety generally resulted in a fall in activity.

Keywords cardiotonic agent; structure–activity relationship; piperidine; quinazoline; imidazolidinone; imidazolidinethione

In previous papers, we described the synthesis and cardiotonic activity of some quinazoline, phthalazine and 1,2,3-benzotriazine derivatives.[1] In the course of our studies, we found that 1-[1-(6,7-dimethoxy-4-quinazolinyl)-4-piperidinyl]-2-imidazolidinone (**1**) showed potent cardiotonic activity. In order to define the structural requirements for cardiotonic activity of the series, we have attempted to modify **1** by replacing the 2-oxoimidazolidinyl group with 3-substituted 2-oxoimidazolidinyl or 2-thioxoimidazolidinyl groups. The paper describes the synthesis and pharmacological activities of some 6,7-dimethoxyquinazoline derivatives of formula A (Chart 1), as summarized in Tables I and II.



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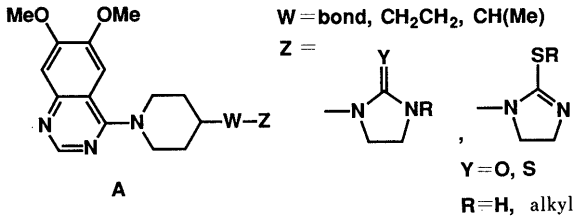


A

Chart 1

Chemistry

Depending upon the substituents at the 4-position of the piperidine, five different synthetic routes (Charts 2—6) were used to synthesize the compounds listed in Tables I and II.

The compounds which have an alkyl chain between the piperidine and the imidazolidinone rings (**20**, **17**) were synthesized by reaction of the chloride **27**[2] with 1-[1- and 1-[2-(4-piperidinyl)ethyl]-2-imidazolidinone (**28**, **29**), respectively, which were prepared from 1-[1- and 1-[2-(4-pyridyl)ethyl]-2-imidazolidinones (**30**, **31**)[3] by catalytic reduction over 5% rhodium on alumina under 3 atm of hydrogen for 2 d at room temperature (Chart 2).

The synthetic sequence leading to the 2-imidazolidinethione (**12**) is outlined in Chart 3. Reduction of the 4-piperidone (**33**)[4] with $NaBH_4$ in the presence of 10 eq of ethylenediamine and subsequent cyclization with CS_2 of the resulting **34** afforded the thione **12**.

Alkylation of **1**, **17** and **20** with alkyl halides in the presence of NaH gave the 3-alkyl-2-imidazolidinones (**2**—**7**, **18**, **19** and **21**, **22**) (Chart 4). On the other hand, alkylation of **12** with alkyl halides under a similar reaction condition afforded the *S*-alkylated compounds (**23**—**26**) with a small amount of the *N*-alkylated isomers (**13**—**16**) (Chart 5). In the proton nuclear magnetic resonance (^{1}H-NMR) spectra, the *S*-methyl derivative (**23**) showed the methyl proton signal at 2.60 ppm and the *N*-methyl isomer (**13**) showed it at 3.18 ppm.

The 3-(2-hydroxyethyl)-2-imidazolidinone (**8**) was prepared from the reaction of **27** with 1-(4-piperidinyl)-3-(2-hydroxyethyl)-2-imidazolidinone (**32**).[5] Compound **8** was acetylated with Ac_2O to give **9** and mesylated with

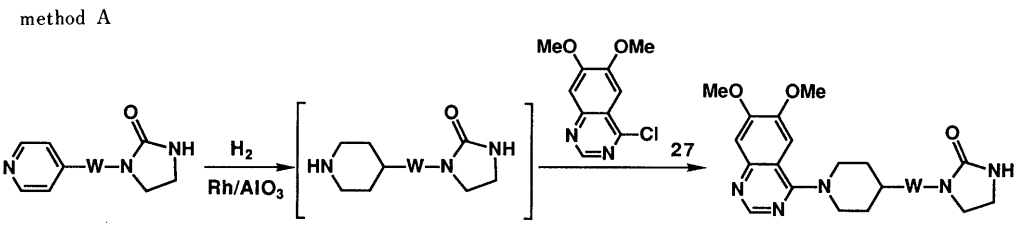


Chart 2

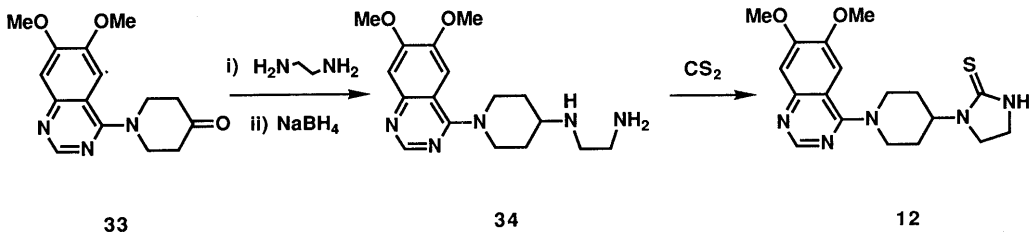


Chart 3

method B

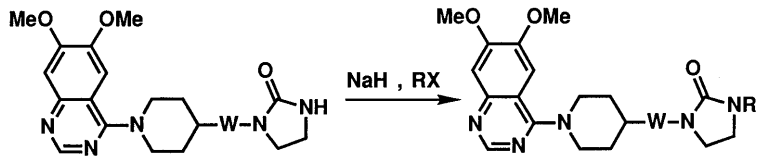


Chart 4

method C

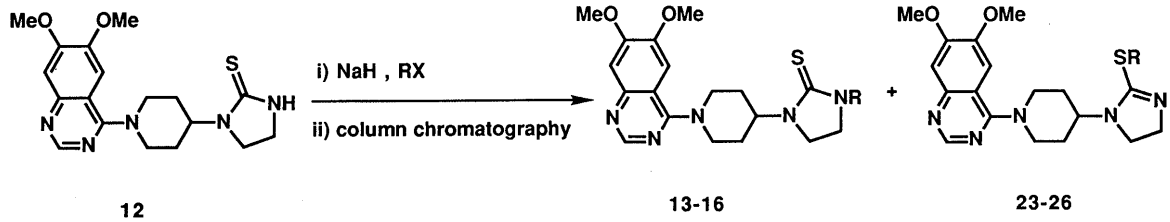


Chart 5

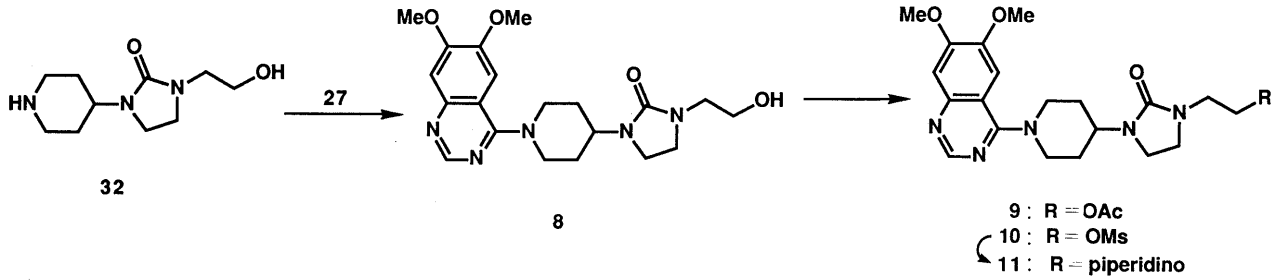


Chart 6

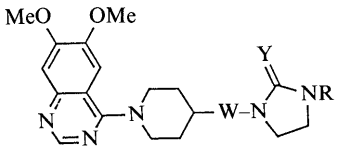
CH_3SO_2Cl to give **10**. Compound **10** reacted with piperidine to give the piperidinoethyl derivative **11** (Chart 6).

Biological Results

Cardiotonic activities of the compounds listed in Tables I and II were evaluated in anesthetized open chest dogs using the procedures previously described.[1a] The results of the test are shown in Table III. The positive cardiotonic activity of the compounds was determined by measuring percent increase in maximum *dP/dt* left ventricular pressure (LV*dP/dt* max, Δ%) after i.v. administration (1.0 mg/kg) in anesthetized mongrel dogs of either sex (8—15 kg). The potency of cardiotonic activity of the test compounds was compared with milrinone (0.1 mg/kg i.v.).[6] Relative potency was calculated as the ratio of LV*dP/dt* max of each compound to that of milrinone (milrinone = 1) in the same dogs.

With respect to the effect of *N*-substituents on the 2-oxoimidazolidine ring, introduction of an alkyl group such as Me (**2**), Et (**3**), *n*-Pr (**4**), allyl (**6**) and methoxymethyl (**7**) provided relatively potent compounds. Benzyl (**5**), 2-hydroxyethyl (**8**) and 2-piperidinoethyl (**11**) substituents led to weakly active compounds. As regards presence of an alkyl group between the piperidine and the 2-oxoimidazolidine rings, introduction of an alkyl group generally resulted in a fall in activity. The 1-ethyl derivatives (**20**—**22**) exhibited a weaker activity than the corresponding 2-ethyl derivatives (**17**—**19**). The imidazolidinethione (**12**) showed relatively potent and long-lasting activity. Marked loss of activity was observed on introduction of the alkylthio group at the 2-position of the imidazolidine ring (**24**—**26**). These results indicate that the 2-oxo and the 2-thioxo groups

TABLE I



Compd. No.	W	Y	R Reagent	Method Yield (%)	mp (°C) (Crystn. solv.)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
2	—	O	Me MeI	B 56	201—202 (MeOH–H_2O)	$C_{19}H_{25}N_5O_3$	61.44	6.78	18.86	61.25	6.76	18.82
3	—	O	Et EtI	B 36	183—185 (MeOH–H_2O)	$C_{20}H_{27}N_5O_3$	62.32	7.06	18.17	61.97	6.91	18.33
4	—	O	*n*-Pr *n*-PrI	B 69	204—206 (MeOH–H_2O)	$C_{21}H_{29}N_5O_3$	63.13	7.32	17.53	62.83	7.27	17.45
5	—	O	Bzl BzlBr	B 52	195—197.5 (MeOH–H_2O)	$C_{25}H_{29}N_5O_3$	67.09	6.53	15.65	67.11	6.63	15.29
6	—	O	$CH_2CH=CH_2$ $CH_2=CHCH_2Br$	B 66	171.5—172.5 (MeOH–H_2O)	$C_{21}H_{27}N_5O_3$	63.45	6.85	17.62	63.27	6.88	17.61
7	—	O	CH_2OMe $MeOCH_2Cl$	B 60	178 (MeOH–H_2O)	$C_{20}H_{27}N_5O_4$	59.84	6.78	17.44	60.06	6.95	17.33
8	—	O	CH_2CH_2OH	[b] 99	191.5—193 (MeOH–Et_2O)	$C_{20}H_{27}N_5O_4$	59.84	6.78	17.44	59.70	6.74	17.21
9	—	O	CH_2CH_2OAc	[b] 81	162.5—164 (MeOH–Et_2O)	$C_{22}H_{29}N_5O_5$	59.58	6.59	15.79	59.67	6.63	15.63
10	—	O	CH_2CH_2OMs	[b] 85	229—233 (MeOH–Et_2O)	$C_{21}H_{29}N_5O_6S$	52.59	6.10	14.61	52.80	6.33	14.27
11	—	O	2-Piperidinoethyl	[b] 54	147—149 (MeOH–Et_2O)	$C_{25}H_{36}N_6O_3$	64.08	7.74	17.94	64.23	7.93	17.75
12	—	S	H	[b] 73[c]	255 (MeOH)	$C_{18}H_{23}N_5O_2S$	57.89	6.21	18.75	58.26	6.43	18.37
13	—	S	Me MeI	C 1	218 (MeOH–H_2O)	$C_{19}H_{25}N_5O_2S$	58.89	6.50	18.07	58.70	6.32	17.72
14	—	S	Et EtI	C 16	214 (MeOH–H_2O)	$C_{20}H_{27}N_5O_2S$	59.83	6.78	17.44	59.48	6.65	17.74
15	—	S	*n*-Pr *n*-PrI	C 14	192—194 (MeOH–H_2O)	$C_{21}H_{29}N_5O_2S$	60.69	7.03	16.85	60.73	6.98	16.58
16	—	S	$CH_2CH(OEt)_2$ $(EtO)_2CHCH_2Br$	C 42	128—129 (MeOH–H_2O)	$C_{24}H_{35}N_5O_4S\cdot H_2O$	56.78	7.35	13.80	56.61	7.14	13.68
17	$-CH_2CH_2-$	O	H **31**	A 41[d]	237—239 (MeOH–H_2O)	$C_{20}H_{27}N_5O_3$	62.32	7.06	18.17	62.29	7.28	17.94
18	$-CH_2CH_2-$	O	Me MeI	B 60	156.5—160 (MeOH–H_2O)	$C_{21}H_{29}N_5O_3$	63.14	7.32	17.53	62.99	7.53	17.57
19	$-CH_2CH_2-$	O	Et EtI	B 57	137.5—139.5 ($CHCl_3$–Et_2O)	$C_{22}H_{31}N_5O_3$	63.90	7.56	16.93	63.83	7.86	16.76
20	–CH(Me)–	O	H **30**	A 51[e]	205—206 (MeOH–Et_2O)	$C_{20}H_{27}N_5O_3$	62.32	7.06	18.17	62.49	7.41	18.10
21[a]	–CH(Me)–	O	Me MeI	B 35	209—209.5 (MeOH–Et_2O)	$C_{21}H_{29}N_5O_3\cdot HCl$	57.86	6.94	16.06	58.08	6.94	15.68
22	–CH(Me)–	O	Et EtI	B 53	148.5—149 (MeOH–Et_2O)	$C_{22}H_{31}N_5O_3$	63.90	7.56	16.93	63.99	7.54	16.76

a) As HCl salt. *b*) See Experimental section. *c*) From **33**. *d*) From **31**. *e*) From **30**.

are preferable for improved activity to the 2-alkylthio group.

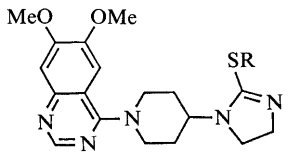
Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were measured on a Shimadzu IR-27G spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a Varian EM-390 and a JNM-PS-100 spectrometer using tetramethylsilane (TMS) as an internal standard.

Method A. 1-[2-{1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl}ethyl]-2-imidazolidinone (17) A mixture of **31** (2.2 g, 11 mmol) and 5% Rh on alumina (0.44 g) in 1 N HCl (20 ml) was shaken in a Parr apparatus under 3 atm H_2 pressure at room temperature for 2 d. After removal of the catalyst, the filtrate was concentrated. The residue was dissolved in EtOH (30 ml), then **27** (1.5 g, 6.7 mmol) and Et_3N (2.0 ml, 14 mmol) were added to the solution which was stirred under reflux for 15 min. After cooling the mixture, the precipitated crystals were collected by filtration, washed successively with EtOH and water, then dried to give **17** (1.8 g, 41% from **31**). An analytical sample was recrystallized from MeOH–Et_2O. IR (KBr): 1700, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.67 (1H, s, Ar-H), 7.22 (1H, s, Ar-H), 7.10 (1H, s, Ar-H), 5.01 (1H, br, NH), 4.28—1.50 (13H, m, piperidine, $-CH_2CH_2-$), 4.03, 4.00 (3H, each, s, CH_3O), 3.43 (4H, s, imidazolidine). Compound **20** was obtained by a similar procedure as described above except that **30** was used instead of **31**.

1-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]-2-imidazolidinethione (12) $NaBH_4$ (0.49 g, 13 mmol) was added portionwise to a stirred mixture of **33** (3.0 g, 11 mmol) and ethylenediamine (6.5 g, 108 mmol) in MeOH (50 ml) at room temperature, then the mixture was concentrated. The oily residue was partitioned between water and $CHCl_3$, and the extract was washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. The oily residue was dissolved in EtOH (15 ml), then Et_3N (2.1 g,

TABLE II



Compd. No.	R Reagent	Method Yield (%)	mp (°C) (Crystn. solv.)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
23	Me	C	205—206	$C_{19}H_{25}N_5O_2S$	58.89	6.50	18.07	59.04	6.32	18.30
	MeI	53	(EtOH–H_2O)							
24	Et	C	164—165	$C_{20}H_{27}N_5O_2S$	59.83	6.78	17.44	59.44	6.73	17.50
	EtI	41	(EtOH–H_2O)							
25	*n*-Pr	C	153—154.5	$C_{21}H_{29}N_5O_2S$	60.69	7.03	16.85	60.50	6.92	16.84
	n-PrI	40	(EtOH–H_2O)							
26	$CH_2CH(OEt)_2$	C	103—105	$C_{24}H_{35}N_5O_4S \cdot H_2O$	56.78	7.35	13.80	66.71	6.95	14.02
	$(EtO)_2CHCH_2Br$	21	(EtOH–H_2O)							

TABLE III. Biological Activity of Some Quinazoline Derivatives in Anesthetized Dogs

Compd. No.	Cardiotonic activity LV*dP/dt* max[a] (*Δ*%)		Relative[b] potency	Duration (min)
2	43.5±14.2		1.14	>60
3	47.0± 1.7		0.83	40
4	60.3±19.9		0.93	30—45
5	17.0± 6.9		0.32	10—15
6	43.3±13.2		0.84	45
7	34.4±11.8		0.72	45
8	14.9	(2)	0.28	15
11	18.5	(2)	0.35	10
12	42.7± 1.1		0.87	>60
15	24.7± 4.4		0.42	15
16	24.4± 2.9		0.45	15
17	31.5	(2)	0.43	20
18	44.6	(2)	0.61	20
19	49.6	(2)	0.67	20
20	14.5	(2)	0.28	10
21	20.6	(2)	0.39	10
22	6.5	(2)	0.12	5
24	2.3± 1.2		—	—
25	6.5± 1.0		0.15	15
26	14.4± 1.3		0.30	5—10

a) Each value represents the mean ± standard error of triplicate experiments except where otherwise noted in parentheses. *b*) Compared to the percent increase in LV*dP/dt* max observed with milrinone (0.1 mg/kg) in the same dogs.

21 mmol) and CS_2 (3.0 ml) were added to the solution. The mixture was stirred for 15 h under reflux. After cooling the reaction mixture, the precipitated crystals were collected by filtration to give crude crystals of **12** which were recrystallized from MeOH to afford pure **12** (3.0 g, 73% from **33**). IR (KBr): 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.60 (1H, s, Ar-H), 8.10 (1H, br s, NH), 7.24 (1H, s, Ar-H), 7.15 (1H, s, Ar-H), 4.30—1.60 (13H, m, piperidine, imidazolidine), 4.08, 4.06 (3H, each s, CH_3O).

Method B. 1-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]-3-methyl-2-imidazolidinone (2) MeI (0.71 g, 5.0 mmol) was added dropwise to a stirred mixture of **1** (1.5 g, 4.2 mmol) and 60% NaH (0.37 g, 8.4 mmol) in dimethylsulfoxide (DMSO) (10 ml). The reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and concentrated. The residual crystalline was recrystallized from EtOH–Et_2O to afford **2** (0.86 g, 56%). IR (KBr): 1685, 1510 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.70 (1H, s, Ar-H), 7.28 (1H, s, Ar-H), 7.15 (1H, s, Ar-H), 4.40—1.78 (9H, m, piperidine), 4.08, 4.06, (3H, each s, CH_3O), 3.26 (4H, br s, imidazolidine), 2.73 (3H, s, NCH_3). A similar procedure as that described above was carried out except for use of another alkylating agent listed in Table I instead of MeI to give compounds **3**—**7**. Compounds **18**, **19** and **21**, **22** were also obtained starting from **17** and **20**, respectively.

Method C. 1-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]-3-methyl-2-imidazolidinethione (13) and 1-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]-2-methylthioimidazoline (23) MeI (0.33 ml, 5.2 mmol) was added to a mixture of **12** (0.98 g, 2.6 mmol) and 60% NaH (0.25 g, 5.2 mmol) in dimethylformamide (DMF) (5 ml). The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$, then evaporated under reduced pressure. The crude residue was chromatographed on a silica gel column (40 g). The less polar isomer was eluated with 2% MeOH–$CHCl_3$ to give **13** as crystals which were recrystallized from MeOH–water to give pure **13** (15 mg, 1%). IR (KBr): 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.72 (1H, s, Ar-H), 7.24 (1H, s, Ar-H), 7.10 (1H, s, Ar-H), 4.90—1.70 (9H, m, piperidine), 4.02, 3.98 (3H, each, s, CH_3O), 3.58 (4H, s, imidazolidine), 3.18 (3H, s, CH_3). The more polar isomer was eluated with 16% MeOH–$CHCl_3$ to afford **23** as crystal which was recrystallized from MeOH–water to give pure **23** (0.56 g, 53%), IR (KBr): 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.78 (1H, s, Ar-H), 7.32 (1H, s, Ar-H), 7.18 (1H, s, Ar-H), 4.50—1.80 (9H, m, piperidine), 4.04, 4.00 (3H, each, s, CH_3O), 3.70 (4H, m, imidazoline), 2.60 (3H, s, CH_3). A similar procedure as described above was effected except that another alkylating agent listed in Tables I and II was used instead of MeI to give compounds **14**—**16** and **24**—**26**.

1-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]-3-(2-hydroxyethyl)-2-imidazolidinone (8) A mixture of **27** (2.0 g, 8.8 mmol), **32** (2.2 g, 8.8 mmol) and Et_3N (3.0 ml, 23 mmol) in MeOH (50 ml) was stirred for 2 h at 60 °C. Water was added to the mixture and the precipitated crystals were collected by filtration to give crude **8**. Recrystallization from MeOH–Et_2O afforded pure **8** (3.5 g, 99%). IR (KBr): 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.66 (1H, s, Ar-H), 7.24 (1H, s, Ar-H), 7.12 (1H, s, Ar-H), 4.60 (1H, br, OH), 4.45—1.70 (13H, m, piperidine, $-CH_2CH_2-$), 4.01, 3.98 (3H, each, s, CH_3O), 3.40 (4H, br s, imidazolidine).

1-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]-3-(2-acetoxyethyl)-2-imidazolidinone (9) A mixture of **8** (0.30 g, 0.75 mmol), Et_3N (0.14 ml, 1.0 mmol), 4-dimethylaminopyridine (5 mg) and Ac_2O (0.075 ml, 0.80 mmol) in CH_3CN (20 ml) was stirred for 1 h at room temperature. The reaction mixture was concentrated and the residue was partitioned between $CHCl_3$ and water. The organic layer was washed with water, dried over $MgSO_4$ and evaporated. The crystalline residue was suspended in MeOH–Et_2O and collected by filtration to afford crude **9** (0.27 g, 81%). An analytical sample was recrystallized from MeOH–Et_2O. IR (KBr): 1740, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.67 (1H, s, Ar-H), 7.26 (1H, s, Ar-H), 7.12 (1H, s, Ar-H), 4.46—1.78 (9H, m, piperidine), 4.23 (2H, t, J=8 Hz, $-CH_2O-$), 4.02, 3.99 (3H, each, s, CH_3O), 3.48 (2H, t, J=8 Hz, $-NCH_2-$), 3.39 (4H, s, imidazolidine), 2.06 (3H, s, $OCOCH_3$).

1-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]-3-(2-methanesulfonyloxyethyl)-2-imidazolidinone (10) A mixture of **8** (0.30 g, 0.75 mmol), MsCl (0.062 ml, 0.80 mmol), Et_3N (0.14 ml, 1.0 mmol) and 4-dimethylaminopyridine (50 mg) in CH_3CN (20 ml) and tetrahydrofuran (THF) (10 ml) was stirred for 1 h at room temperature, then concentrated. The residue

was mixed with water and extracted with $CHCl_3$. Usual workup of the extract afforded crystals which were recrystallized from MeOH–Et_2O to give **10** (0.31 g, 85%). IR (KBr): 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.66 (1H, s, Ar-H), 7.26 (1H, s, Ar-H), 7.12 (1H, s, Ar-H), 4.30—1.75 (9H, m, piperidine), 4.02, 3.98 (3H, each, s, CH_3O), 3.55 (2H, t, J=7 Hz, $-CH_2O-$), 3.39 (2H, t, J=7 Hz, $-NCH_2-$), 3.40 (4H, br s, imidazolidine), 3.02 (3H, s, CH_3SO_2).

1-[1-(6,7-Dimethoxy-4-quinazolinyl)-4-piperidinyl]-3-(2-piperidinoethyl)-2-imidazolidinone (11) A mixture of **10** (0.30 g, 0.63 mmol), piperidine (0.19 ml, 1.9 mmol) and Et_3N (0.40 ml, 3.0 mmol) in DMF (20 ml) was stirred for 7 h at 60 °C. The reaction mixture was evaporated under reduced pressure and the residue was diluted with water, then extracted with $CHCl_3$. Usual workup of the extract gave crystals which were recrystallized from MeOH–water to give **11** (0.16 g, 54%). IR (KBr): 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.64 (1H, s, Ar-H), 7.26 (1H, s, Ar-H), 7.14 (1H, s, Ar-H), 4.45—1.40 (23H, m, piperidines, $-CH_2CH_2-$), 4.08, 4.06 (3H, each, s, CH_3O), 3.38 (4H, br s, imidazolidine).

References and Notes

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